We Claim:

1.   A method of modulating a biological response in a cell, the method comprising

5   contacting the cell with at least one agent that modulates the expression or activity of

Errα or Gabp, wherein the biological response is

        (a)   expression of at least one OXPHOS gene;

        (b)   mitochondrial biogenesis;

        (c)   expression of Nuclear Respiratory Factor 1 (NRF-1);

10   (d)   β-oxidation of fatty acids;

        (e)   total mitochondrial respiration;

        (f)   uncoupled respiration;

        (g)   mitochondrial DNA replication;

        (h)   expression of mitochondrial enzymes; or

15   (i)   skeletal muscle fiber-type switching.

2.   The method of claim 1, wherein the agent increases at least one of the biological

responses.

20   3.   The method of claim 1, wherein the agent modulates the formation of a complex between

a PGC-1 polypeptide and (i) an Errα polypeptide; or (ii) a Gabp polypeptide.

4.   The method of the preceding claim, wherein the agent increases the formation of the

complex.

25

5.   The method of claim 1, wherein the agent is an Errα antagonist or an agonist.

6.   The method of claim 1, wherein the agent modulates the expression level or the

transcriptional activity of an Errα polypeptide, a Gabp polypeptide, or of both.

30

7.   The method of claim 1, comprising contacting the cell with two agents, wherein one

agent modulates the expression or activity of Errα and the other agent modulates the expression or activity of Gabp.

8.   The method of claim 10 or 11, wherein modulates consists of increasing.

9.   The method of claim 10 or 11, wherein modulates consists of decreasing.

10.   The method of claim 1, wherein the cell is a skeletal muscle cell, a smooth muscle cell, a cardiac muscle cell, a hepatocyte, an adipocyte, a neuronal cell or a pancreatic cell.

11.   The method of claim 1, wherein the cell is in an organism.

12.   The method of the preceding claim, wherein the organism is a mammal.

13.   The method of the preceding claim, wherein the mammal is a human.

14.   The method of the preceding claim, wherein the human is afflicted with a disorder characterized by reduced mitochondrial activity.

15.   The method of the preceding claim, wherein the disorder is diabetes, obesity, cardiac myopathy, aging, coronary atherosclerotic heart disease, diabetes mellitus, Alzheimer's Disease, Parkinson's Disease, Huntington's disease, dystonia, Leber's hereditary optic neuropathy (LHON), schizophrenia, myodegenerative disorders such as "mitochondrial encephalopathy, lactic acidosis, and stroke" (MELAS). and "myoclonic epilepsy ragged red fiber syndrome" (MERRF), NARP (Neuropathy; Ataxia; Retinitis Pigmentosa), MNGIE (Myopathy and external ophthalmoplegia, neuropathy; gastro-intestinal encephalopathy, Kearns-Sayre disease, Pearson's Syndrome, PEO (Progressive External Ophthalmoplegia), congenital muscular dystrophy with mitochondrial structural abnormalities, Wolfram syndrome, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy Deafness, Leigh's Syndrome, fatal infantile myopathy with severe mitochondrial DNA (mtDNA) depletion, benign "later-onset" myopathy with moderate reduction in mtDNA,

dystonia, medium chain acyl-CoA dehydrogenase deficiency, arthritis, and mitochondrial diabetes and deafness (MIDD), mitochondrial DNA depletion syndrome.

16.   The method of claim 1, wherein the cell is a skeletal muscle cell.

5

17.   A method of determining if an agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function, the method comprising determining if the agent increases:

     (i)   the expression or activity of Errα or Gabp in a cell; or

10

     (ii) the formation of a complex between a PGC-1 polypeptide and (i) an Errα polypeptide; or (ii) a Gabp polypeptide;

wherein an agent that increases (i) or (ii) is a potential target for the treatment of the disorder.

15   18.   A method of identifying an agent that modulates a biological response, the method comprising

     (a) contacting, in the presence of the agent, a PGC-1 polypeptide and an (i) Errα polypeptide, or (ii) a Gabp polypeptide, under conditions which allow the formation of a complex between the PGC-1 polypeptide and (i) the Errα

20

     polypeptide, or (ii) the Gabp polypeptide; and

     (b) detecting the presence of the complex;

wherein an agent that modulates the biological response is identified if the agent increases or decreases the formation of the complex, and wherein the biological response is

25

     (a) expression of the OXPHOS genes;

     (b) mitochondrial biogenesis;

     (c) expression of Nuclear Respiratory Factor 1 (NRF-1);

     (d) β-oxidation of fatty acids;

     (e) total mitochondrial respiration;

30

     (f) uncoupled respiration;

     (g) mitochondrial DNA replication; or

(h) expression of mitochondrial enzymes.

19.   The method of claim 18, wherein the agent increases the formation of the complex, and
       wherein the agent increases the biological response.

20.   The method of claim 19, wherein the agent decreases the formation of the complex, and
       wherein the agent decreases the biological response.

21.   The method of claim 18, wherein the contacting step is performed on a cell.

22.   The method of claim 18, wherein the Gabp polypeptide is a Gabpa polypeptide.

23.   A method of treating or preventing a disorder characterized by reduced mitochondrial
       function, glucose intolerance, or insulin intolerance in a subject, the method comprising
       administering to the subject a therapeutically effective amount of an agent which
           (i) increases the expression or activity of Errα or Gabp or both; or
           (ii) increases the formation of a complex between a PGC-1 polypeptide and (a) an
                 Errα polypeptide; (b) a Gabp polypeptide; or both; or
           (iii) binds to an (a) Errα binding site, or to a (b) Gabpa binding site, and which
                 increases transcription of at least one gene in the subject, said gene having an
                 Errα binding site, a Gabpa binding site, or both.

24.   The method of claim 23, wherein the agent which binds to an (a) Errα binding site, or to
       a (b) Gabp binding site comprises at least one DNA binding domain.

25.   The method of the preceding claim, wherein the DNA binding domain comprises at least
       one zinc-finger.

26.   The method of claim 23, wherein the disorder is obesity or diabetes.

27.   The method of the preceding claim, wherein the diabetes is type 2 diabetes mellitus.

28.   The method of the preceding claim, wherein the subject has elevated gluconeogenesis.

29.   A method of treating or preventing a disorder characterized by reduced mitochondrial
       function, glucose intolerance, or insulin intolerance in a subject, the method comprising
       administering to the subject a therapeutically effective amount of an agent which
       increases the expression or activity of a gene, wherein the gene has an Errα binding site
       or a Gapba binding site.

30.   The method of claim 29, wherein the gene has an Errα binding site and a Gapba binding
       site.

31.   The method of claim 29, wherein the Errα binding site comprises the sequence
       TGACCTTG or CAAGGTCA.

32.   The method of claim 29, wherein the Gapba binding site comprises the sequence
       CTTCCG or CGGAAG.

33.   The method of claim 29, wherein the gene is Errα, Gapba, or any of the genes listed in
       Tables 10-12.

34.   The method of claim 39, wherein the gene is not Errα or Gapba.

35.   A method of reducing the metabolic rate of a subject in need thereof, the method
       comprising administering to the subject a therapeutically effective amount of an agent
       which decreases the expression or activity of at least one of the following:
              (i) Errα;
              (ii) Gabpa;
              (iii) a gene having an Errα binding site, a Gabpa binding site, or both; or
              (iv) a transcriptional activator which binds to an Errα binding site or to a Gabpa
                     binding site;

thereby reducing the metabolic rate of the patient.

36.   The method of claim 35, wherein the subject is afflicted with a viral infection or with cancer.

5

37.   The method of the preceding claim 35, wherein the viral infection is a human immunodeficiency virus infection.

38.   The method of claim 35, wherein the subject is afflicted with cancer cachexia, pulmonary

10   cachexia, cardiac cachexia, Russell's Diencephalic Cachexia, or chronic renal insufficiency.

39.   The method of claim 35, wherein the agent decreases the formation of a complex between a PGC-1 polypeptide and (i) an Errα polypeptide; or (ii) a Gabp polypeptide.

15

40.   The method of claim 35, wherein the agent decreases the expression level or the transcriptional activity of an Errα polypeptide, a Gabp polypeptide, or both.

41.   The method of claim 35, wherein the agent is an Errα antagonist.

20

42.   A method of identifying a susceptibility locus for a disorder that is characterized by reduced mitochondrial function, glucose intolerance, or insulin intolerance in a subject, the method comprising

(i) identifying at least one polymorphisms in a gene, or linked to a gene, wherein

25   the gene (a) has an Errα binding site, a Gabpa binding site, or both; or (b) is Errα, Gabpa, or Gabpb;

(ii) determining if at least one polymorphism is associated with the incidence of the disorder,

wherein if a polymorphism is associated with the incidence of the disorder then the gene

30   having the polymorphism, or the gene to which the polymorphism is linked, is a susceptibility locus.

(iii) identifying a subset of genes, wherein each gene in the subset contains the same DNA sequence motif;

(iv) testing via a nonparametric statistic if the subset of genes are enriched at either the top or the bottom of the ranking;

5

(v) optionally reiterating steps (ii)-(iii) for additional motifs;

(vi) for a subset of genes that is enriched, identifying a transcriptional regulator which binds to a DNA sequence motif that is contained in the subset of genes;

thereby identifying a transcriptional regulator having differential activity between two cells.

10

52.   The method of claim 51, wherein determining the level of expression of a gene in a cell comprises determining the levels of mRNA for the gene in the cell.

53.   The method of the preceding claim, wherein the levels of mRNA are determined using a

15   DNA microarray.

54.   The method of claim 51, wherein identifying a transcriptional regulator which binds to a DNA sequence motif comprises searching a database comprising transcriptional regulators and DNA sequence motifs to which they bind.

20

55.   The method of claim 51, wherein identifying a transcriptional regulator which binds to a DNA sequence motif comprises experimentally identifying a transcriptional regulator which binds to the DNA sequence motif.

25   56.   The method of the preceding claim, wherein experimentally identifying a transcriptional regulator which binds to the DNA sequence motif comprises

(i) identifying, from a library of genes, a transcriptional regulator capable of driving the expression of a selectable marker, wherein the expression of the selectable marker is dependent on binding of the transcriptional regulator to the DNA

30   sequence motif; or

(ii) biochemically purifying the transcriptional regulator based on its affinity for the

43.   The method of claim 42, wherein the gene is anyone of the gene listed on Tables 10-12.

44.   The method of claim 42, wherein the disorder is a metabolic disorder.

45.   The method of the preceding claims, wherein the disorder is diabetes or obesity.

46.   The method of claim 44, wherein the metabolic disorder is a disorder associated with aberrant lipogenesis.

47.   A method of determining if a subject is at risk of developing a disorder which is characterized by reduced mitochondrial function, the method comprising determining if a gene from the subject contains a mutation which reduces the function of the gene, wherein the gene has an Errα binding site, a Gapba binding site, or both, wherein if a gene from the subject contains a mutation then the subject is at risk of developing the disorder.

48.   The method of the preceding claim, wherein the mutation reduces the function of the gene.

49.   The method of claim 47, wherein the disorder is diabetes, obesity, premature aging, cardiomyopathy, a neurodegenerative disease, or retinal degeneration.

50.   The method of claim 47, wherein the gene is any one of the genes listed on Tables 10-12.

51.   A method of identifying a transcriptional regulator having differential activity between an experimental cell and a control cell, the method comprising
        (i)   determining the level of gene expression of at least two genes in the experimental cell and in the control cell;
        (ii) ranking genes according to a difference metric of their expression level in the experimental cell compared to the control cell;

DNA sequence motif.

57.   The method of claim 51, wherein each gene in the subset contains an identical DNA sequence motif in its promoter regions.

5

58.   The method of the preceding claim, wherein the promoter regions are masked promoter regions.

59.   The method of claim 51, wherein the nonparametric statistic is a nonparametric, rank sum statistic.

10

60.   The method of claim 51, wherein the non-parametric statistic is selected from the group consisting of a Kolmogorov-Smirnov, Mann-Whitney or Wald-Wolfowitz.

15   61.   The method of claim 51, wherein the difference metric is a difference in arithmetic means, t-test scores, or signal to noise ratios.

62.   The method of claim 51, wherein the cells are mammalian cells.

20   63.   The method of the preceding claim, wherein the cells are human cells.

64.   The method of claim 51, wherein the cells are primary cells.

65.   The method of claim 51, wherein the experimental cell, the control cell, or both, are derived from a subject.

25

66.   The method of the previous claim, wherein the subject is afflicted with a disorder.

67.   The method of the previous claim, wherein the disorder is a metabolic disorder.

30

68.   The method of claim 66, wherein the disorder is a hyperplastic condition.

69.   The method of the preceding claim, wherein the experimental cell is hyperplastic cells.

70.   The method of claim 51, wherein the experimental cell, but not the control cell, is
5   contacted with a compound.

71.   The method of claim 51, wherein the compound is a drug.

72.   The method of claim 51, wherein the experimental cell is genetically modified.
10

73.   The method of the preceding claim, wherein the experimental cell is genetically modified
        to express a transgene.

74.   The method of the preceding claim, wherein the transgene is a recombinant
15   transcriptional regulator.

75.   The method of the preceding claim, wherein the DNA sequence motif is not a DNA
        binding motif that is bound by the recombinant transcriptional regulator.

20 76.   The method of claim 74, wherein the recombinant transcriptional regulator encodes a
        mutant transcriptional regulator.

77.   The method of claim 74, wherein the recombinant transcriptional regulator encodes a
        mutant transcriptional regulator associated with a disease state.
25

78.   A method of detecting statistically-significant differences in the expression level of at
        least one biomarker belonging to a biomarker set, between the members of a first and of a
        second experimental group, comprising:
            (a) obtaining a biomarker sample from members of the first and the second
30   experimental groups;

(b) determining, for each biomarker sample, the expression levels of at least one biomarker belonging to the biomarker set and of at least one biomarker not belonging to the set;

(c) generating a rank order of each biomarker according to a difference metric of its expression level in the first experimental group compared to the second experimental group;

(d) calculating an experimental enrichment score for the biomarker set by applying a non parametric statistic; and

(e) comparing the experimental enrichment score with a distribution of randomized enrichment scores to calculate the fraction of randomized enrichment scores greater than the experimental enrichment score, wherein a low fraction indicates a statistically-significant difference in the expression level of the biomarker set between the members of the first and of the second experimental group.

79. The method of claim 78, wherein the distribution of randomized enrichment scores is generated by

(i) randomly permutating the assignment of each biomarker sample to the first or to the second experimental group;

(ii) generating a rank order of each biomarker according to the absolute value of a difference metric of its expression level in the first experimental group compared to the second experimental group;

(iii) calculating an experimental enrichment score for the biomarker set by applying a non parametric statistic to the rank order; and

(iv) repeating steps (i), (ii) and (iii) a number of times sufficient to generate the distribution of randomized enrichment scores.

80. The method of claim 78, wherein the distribution of randomized enrichment scores is a normal distribution.

81. The method of claim 78, wherein the difference metric is a difference in arithmetic means.

82.   The method of claim 78, wherein the difference metric is a difference in t-test scores.

83.   The method of claim 78, wherein the difference metric is a difference in signal-to-noise ratio.

84.   The method of claim 78, wherein the non-parametric statistic is selected from the group consisting of a Kolmogorov-Smirnov, Mann-Whitney or Wald-Wolfowitz

84.   The method of claim 79, wherein the non-parametric statistic is selected from the group consisting of a Kolmogorov-Smirnov, Mann-Whitney or Wald-Wolfowitz

85.   The method of claim 78, wherein the biomarker is selected from the group consisting of a nucleic acid, a polypeptide, a metabolite and a genotype.

86.   The method of claim 85, wherein the nucleic acid is mRNA.

87.   The method of claim 85, wherein the nucleic acid is polymorphic DNA.

88.   The method according to claim 78, wherein the expression level is determined using microarray analysis.

89.   The method according to claim 1, wherein the members of the first experimental group have a disorder and the members of the second experimental group do not have the disorder.

90.   The method of claim 89, wherein the disorder is characterized by defective glucose metabolism.

91.   The method of claim 89, wherein the disorder is type II diabetes.

91.   The method according to claim 78, wherein the number of times sufficient to generate a distribution is at least 20 times.

92.   The method of claim 78, wherein the low fraction is less than 0.05.

5

93.   A method of identifying an agent that regulates expression of OXPHOS-CR genes, the method comprising

      (a) contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell; and

10   (b) determining whether the expression of at least two OXPHOS-CR gene products show a coordinate change in the test cell compared to an appropriate control, wherein a coordinate change in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes.

15   94.   The method of claim 93, further comprising determining if the agent also regulates expression of genes which are not OXPHOS-CR genes.

95.   The method of claim 94, wherein one of the genes which are not OXPHOS-CR genes is actin.

20

96.   The method of claim 93, wherein the agent increases the expression of OXPHOS-CR genes.

97.   The method of claim 96, wherein the agent additionally increases the number of

25   mitochondria in the test cell

98.   The method of claim 96, wherein the agent additionally increases coupled oxygen consumption.

30   99.   The method of claim 96, wherein the agent additionally increases mtDNA copy number.

100.   The method of claim 93, wherein the gene products are mRNAs.

101.   The method of claim 93, wherein the gene products are polypeptides.

102.   The method of claim 93, wherein the test cell is a muscle cell or a fat cell.

103.   The method of claim 93, wherein the OXPHOS-CR gene products are selected from the group consisting of NDUFB3, SDHA, NDUFA8, COX7A1, UQCRC1, NDUFC1, NDUFS2, ATP5O, NDUFS3, SDHB, NDUFS5, NDUFB6, COX5B, CYC1, NDUFA7, UQCRB, COX7B, ATP5L, COX7C, NDUFA5, GRIM19, ATP5J, COX6A2 NDUFB5, CYCS, NDUFA2 and HSPC051.

104.   A method of treating impaired glucose tolerance in an individual in need thereof, the method comprising administering to the individual a therapeutically effective amount of an agent which increases the expression level of at least two OXPHOS-CR genes, thereby treating impaired glucose tolerance in the individual.

105.   A method of treating obesity in an individual, comprising administering to the individual a therapeutically effective amount of an agent which increases the expression level of at least two OSPHOS-CR genes, thereby treating obesity in the individual.